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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,467	03/26/2001	Laurent Coen	3495.0174-01	7062

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/816,467	COEN ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,21-23 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,21-23 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2-27-07 has been entered.

Applicants' amendment filed 2-27-07 has been entered. Claims 17, 18 and 21 have been amended. Claims 17, 18, 21-23 and 34-37 are pending and under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 17, 18, 21-23 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "an associated protein" in claims 17 and 18 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered "an associated protein". It is unclear what kind of protein is considered "an associated protein". The specification fails to specifically define the phrase "an associated protein". Claims 21-23 and 34-37 depend from claim 17.

The phrase "amino acids 854-1315 of the tetanus toxin holotoxin" in claims 17 and 18 is vague and renders the claims indefinite. The amino acid sequence and numbering of the

sequence can vary depending on the source of the tetanus toxin holotoxin and which tetanus toxin holotoxin is used as reference. Therefore, amino acids 854-1315 of the tetanus toxin holotoxin can vary depending on what protein sequence is used for reference. Thus, the phrase "amino acids 854-1315 of the tetanus toxin holotoxin" in claims 17 and 18 is vague and renders the claims indefinite. Claims 21-23 and 34-37 depend from claim 17.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 17, 18, 21-23 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "an associated protein" in claims 17 and 18 is considered new subject matter. The amendment filed 2-27-07 points out that support for the amended claim 17 can be found in Example 1, however, no support for the phrase "an associated protein" can be found in Example 1. The specification fails to provide sufficient support for the phrase "an associated protein". Thus, the phrase "an associated protein" is considered new matter. Claims 21-23 and 34-37 depend from claim 17.

The phrase "tetanus toxin **consisting of** a fragment C and a fraction of fragment B having 11 amino acid residues" in claim 17 is considered new subject matter. The amendment filed 2-27-07 points out that support for the amended claim 17 can be found in Example 1, however, no support for the phrase can be found in Example 1. Example 1 shows the preparation of pBS:TTC, which has the **DNA sequence** encoding the TTC fragment representing the amino acids 854-1315 of tetanus holotoxin (see p. 20). However, the construct generated in Example 1 are pGEX:lacZ-TC, pGEX:TTC-lacZ and pCMV:lacZ-TTC, which all encode for beta-gal-TTC fusion protein, as evidenced of the purification of the hybrid protein in Example 2. It is apparent that a hybrid fragment of tetanus toxin **comprising** fragment C and fragment B or a fraction thereof of at least 11 amino acid residues is what is intended throughout the whole specification. No sufficient support can be found in the specification for the phrase "tetanus toxin **consisting of** a fragment C and a fraction of fragment B having 11 amino acid residues", thus, said phrase is considered new matter. Claims 21-23 and 34-37 depend from claim 17.

The phrase "tetanus toxin **consisting of** a fragment C and a fraction of fragment B having 11 amino acid residues...and a fraction of a fragment A devoid of its toxic activity" in claim 18 is considered new subject matter. The amendment filed 2-27-07 points out that support for the amended claim 18 can be found on page 5, lines 1-11, however, no such support for the phrase can be found on page 5. Page 5 states "a hybrid fragment of tetanus toxin **comprising** fragment C and fragment B or a fraction thereof of at least 11 amino acid residue and a fraction of fragment A devoid of its toxic activity." Example 1 shows the preparation of pBS:TTC, which has the **DNA sequence** encoding the TTC fragment representing the amino acids 854-1315 of tetanus holotoxin (see p. 20). However, the construct generated in Example 1 are pGEX:lacZ-

TC, pGEX:TTC-lacZ and pCMV:lacZ-TTC, which all encode for beta-gal-TTC fusion protein, as evidenced of the purification of the hybrid protein in Example 2. It appears that a hybrid fragment of tetanus toxin **comprising** fragment C and fragment B or a fraction thereof of at least 11 amino acid residues and a fraction of fragment A is what is intended throughout the whole specification. No sufficient support can be found in the specification for the phrase "tetanus toxin **consisting of** a fragment C and a fraction of fragment B having 11 amino acid residues...and a fraction of a fragment A devoid of its toxic activity", thus, said phrase is considered new matter.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 17 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) in view of Fairweather et al., 1995 (US Patent 5,443,966).

Claims 17 and 21 are directed to a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin), wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment.

Fishman teaches that C-fragment of tetanus toxin (CF) has been studied as a carrier for delivery of therapeutic proteins to neurons and CF retains much of the capacity of tetanus toxin for binding and transport by neurons. Fishman compares full-length tetanus toxin (TTX) and CF in its capacity to bind and be internalized by neurons by ELISA and shows that TTX is superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization. Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons (last 4 lines).

Fishman does not teach a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin).

Fairweather teaches construction of expression plasmid pTet18 expressing a polypeptide which comprises 121 residues of B fragment and all 451 carboxy-terminal residues of C

fragment of tetanus toxin, transfection of E. coli cells with said expression plasmid, and culturing of the transfected E. coli cells. Fairweather assays expressed tetanus hybrid protein by SDS-PAGE gel and Western blotting using rabbit anti-C fragment sera (e.g. column 8). Since the specification fails to specifically define the term "active molecule", therefore, the solution containing the expressed tetanus hybrid protein during the assay is considered an active molecule. Further, claims 17 and 21 are product claims and Fairweather teaches every limitation of the claimed product. Thus, it is inherent that the tetanus hybrid protein taught by Fairweather has the ability to transfer in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse.

It would have been obvious for one of ordinary skill in the art at the time of the invention to prepare a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin) because CF retains much of the capacity of tetanus toxin for binding and transport by neurons and Fishman shows that TTX is superior to CF in the capacity for neuronal binding and internalization and Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons. Fairweather teaches preparation of a polypeptide which comprises 121 residues of B fragment and all 451 carboxy-terminal residues of C fragment of tetanus toxin. Thus, it would be obvious to one of ordinary skill to prepare the claimed hybrid fragment in view of the teachings of Fishman and Fairweather.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce a hybrid protein that retains much of the capacity of

tetanus toxin for binding and transport by neurons as CF but is superior to CF as taught by Fishman with reasonable expectation of success.

9. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) and Fairweather et al., 1995 (US Patent 5,443,966) as applied to claims 17 and 21 above, and further in view of Hohne-Zell et al., 1993 (FEBS Letters, Vol. 336, No. 1, p. 175-180).

Claim 18 is directed to a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin), and a fraction of a fragment A devoid of its toxic activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between amino acids 225 and 245, wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse.

The teachings of Fishman and Fairweather are as discussed above. Fishman and Fairweather do not specifically teach the zinc-binding motif located in the central part of the chain between amino acids 225 and 245.

Hohne-Zell teaches zinc and the putative zinc-binding domain constitute the active site of the tetanus toxin light chain and replacement of histidine (position 233) by cysteine or valine and of glutamate (position 234) by glutamine completely abolished the activity of light chain on calcium induced catecholamine release (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to generate claimed hybrid fragment because modifying the composition of Fishman et al. by replacing the polypeptide with a larger fragment of tetanus toxin (in addition to C fragment) was better in delivering a molecule to neurons and also because C-fragment of the tetanus toxin alone is not toxic and the toxic portion of the protein resides in the amino terminal, and in combination with the teaching of Hohne-Zell that the putative zinc-binding domain constitutes the active site of the tetanus toxin light chain would make it obvious for one of ordinary skill to remove said zinc-binding domain when generating a tetanus toxin fragment for neuron specific transport.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a tetanus hybrid protein capable of retrograde transport as a carrier molecule for neuron specific protein transfer in vivo as taught by Fishman with reasonable expectation of success.

10. Claims 17, 21, 23, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) and Fairweather et al., 1995 (US Patent 5,443,966) as applied to claims 17 and 21 above, and further in view of Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15).

Claims 17, 21, 23, 34 and 35 are directed to a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin), wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid

fragment. Claims 23, 34 and 35 specify the active molecule is a polynucleotide encoding a protein and said polynucleotide further comprises a promoter capable of expression in neurons or further comprises an enhancer.

The teachings of Fishman and Fairweather are as discussed above. Fishman and Fairweather do not specifically teach a hybrid fragment of tetanus toxin in association with a polynucleotide under the control of a promoter and/or an enhancer.

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo, and the foreign gene can be specifically controlled by the gene's promoter. The toxic portion of the protein resides in the amino terminal (e.g. p. 3 and 4). The non-toxic portion of tetanus toxin (C fragment) can be covalently attached to polylysine whose positive charge serves as a bridge to the non-covalent, electrostatic binding of the negatively charged DNA (e.g. p. 4). Mueller lists neuronal cells that can be used for gene delivery in vitro (see Table 1). Mueller also teaches using RSV promoter for neuron-specific expression of beta-galactosidase (e.g. p. 9).

It would have been obvious for one of ordinary skill at the time of the invention to associated the claimed hybrid fragment with a polynucleotide because Fishman teaches that atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons, and Mueller teaches that the tetanus C-fragment can be used to complex with DNA for neuron specific gene transfer in vivo and use of RSV promoter for said gene transfer.

One ordinary skill at the time the invention was made would have been motivated to do so in order to generate a tetanus hybrid protein capable of retrograde transport as a carrier molecule for neuron specific gene transfer in vivo as taught by Mueller with reasonable expectation of success.

11. Claims 17, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman et al., 1996 (Society for Neuroscience Abstracts, Vol. 22, No. 1-3, pp. 1705) and Fairweather et al., 1995 (US Patent 5,443,966) as applied to claims 17 and 21 above, and further in view of Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) and Khan et al., 1995 (WO 95/04151).

Claims 17, 21 and 22 are directed to a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin), wherein the hybrid fragment is capable of transferring in vivo a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, and a composition comprising an active molecule in association with said hybrid fragment. Claim 22 specifies the active molecule is a protein as recited.
The teachings of Fishman and Fairweather are as discussed above. Fishman and Fairweather do not specifically teach association of the recited proteins with the claimed hybrid fragment of tetanus toxin.

Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde) as a carrier molecule for neuron specific gene transfer in vivo. The non-

toxic portion of tetanus toxin (C fragment) can be covalently attached to polylysine whose positive charge serves as a bridge to the non-covalent, electrostatic binding of the negatively charged DNA (e.g. p. 4). Mueller lists neuronal cells that can be used for gene delivery in vitro (see Table 1). Mueller also teaches using RSV promoter for neuron-specific expression of beta-galactosidase (e.g. p. 9).

Khan teaches construction of a DNA construct comprising a DNA sequence encoding a fusion protein of the formula: TetC-(Z)a-Het, wherein the TetC is the C fragment of tetanus toxin and Het is a heterozygous protein (e.g. abstract). Khan teaches using the DNA construct in producing a fusion protein and the use of said fusion protein as a vaccine (e.g. p. 4).

It would have been obvious for one of ordinary skill in the art at the time of the invention to associate the recited proteins in claim 22 with the claimed hybrid fragment of tetanus toxin because Fishman suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons and Khan teaches association of the C fragment of tetanus toxin with any heterozygous protein, and further, most of the proteins recited in claim 22 are expressed in neurons and Mueller teaches using the C-fragment as a carrier molecule for neuron specific gene transfer.

One having ordinary skill in the art at the time the invention was made would have been motivated to do so in order to deliver the protein as a vaccine as taught by Khan or deliver the therapeutic protein to neurons as taught by Mueller and Fishman with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER